LETTERS TO THE EDITOR

Ultrasound guided percutaneous thrombin injection for the treatment of iatrogenic pseudoaneurysms

EDITOR,—Elford and colleagues recently described rapid and spectacular thrombotic occlusion of an iatrogenic axillary artery pseudoaneurysm following injection of thrombin.[1] The authors concluded that this treatment is "safe" and that it should be considered as the treatment of choice for iatrogenic pseudoaneurysm. Although we agree that thrombin injection is promising, there are important safety issues to address before this treatment can be adopted routinely.

There are little safety data on the immunological effects of these products. Fibrinogen/thrombin products are widely used to help achieve haemostasis during complex cardiac surgery. A recent study of 21 patients undergoing cardiothoracic surgery with fibrin glue (bovine fibrinogen clotted with bovine thrombin) demonstrated IgM and IgG antibodies to bovine thrombin, fibrinogen and factor V in every patient.[2] Although there were no bleeding complications reported in this study, these antibodies can cross react with their human counterparts and result in severe haemorrhagic complications.[3] Antibodies have also been detected after administration of topical bovine thrombin during dental procedures.[4] As direct intravascular injection may result in a more intense immunological and haemostatic response, caution appears to be appropriate until immunologically compatible human thrombin is routinely available.

Many pseudoaneurysms occur after coronary interventional procedures and optimal timing of thrombin treatment has yet to be determined. Thrombotic complications following administration of intravascular bovine thrombin have been described[5] which may have resulted from leakage of thrombin from the pseudoaneurysm into the systemic circulation, although other mechanisms are also possible.[5] Circulating thrombin should rapidly be diluted or neutralised by thrombomodulin and antithrombin III, but potentially catastrophic exposure of the coronary lesion to activated thrombin may be possible. Some pseudoaneurysms may resolve spontaneously after discontinuation of systemic anticoagulation, despite oral antiplatelet agents. Therefore our practice is to use thrombin injection for femoral pseudoaneurysm resistant to ultrasound guided compression, and treatment is deferred until 48 hours after intervention.

We conclude that thrombin injection using ultrasound guidance is poised to replace surgical exploration as the second line treatment for iatrogenic pseudoaneurysm but, particularly for femoral pseudoaneurysm after coronary intervention, further data are necessary before ultrasound guided compression can be abandoned.

J D FERGUSON
A P BANNING
Department of Cardiology
John Radcliffe Hospital
Oxford OX3 9DU, UK

1 Elford J, Burrel C, Roobottom C. Ultrasound guided percutaneous thrombin injection for the treatment of iatrogenic pseudoaneurysms. *Heart* 1999;**82**:526–7.
2 Carroll JF, Moskowitz KA, Edward NM, *et al*. Immunological assessment of patients treated with bovine fibrinogen as a hemostatic agent. *Thromb Haemost* 1996;**76**:925–31.
3 Chouhan VD, De la Cadena RA, Nagaswami C, *et al*. Simultaneous occurrence of human antibodies directed against fibrinogen, thrombin and factor V following the exposure to bovine thrombin: effects on blood coagulation, protein C activation and platelet function. *Thromb Haemost* 1997; **77**:343–49.
4 Muntean W, Zeng W, Edlinger G, *et al*. Severe bleeding due to factor V inhibitor after repeated operation using fibrin sealant containing bovine thrombin. *Thromb Haemost* 1997;**77**:1223.
5 Lennox A, Griffin M, Nicolaides A, *et al*. Regarding "Percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms". *J Vasc Surg* 1998;**28**:1120–1.

This letter was shown to the authors who reply as follows:

While we agree that the intravascular use of thrombosis inducing agents is relatively recent, all of the cases to which Ferguson and Banning refer[1–3] involved the use of bovine thrombin. The Tisseel Kit (Immuno Ag, Vienna) consists of Tisseel, a sealer protein concentrate containing bovine aprotinin, together with human thrombin and calcium chloride solution. We reconstitute the human thrombin using the calcium chloride solution, and inject this. We do not use the sealer protein concentrate, relying instead on the patient's own coagulation factors to form a clot. The manufacturers of the Tisseel Kit confirm that there is, therefore, no risk of antibodies to bovine proteins being formed.

The authors also raise concerns about thrombotic complications that may have resulted from leakage of thrombin out of a pseudoaneurysm into the systemic circulation.[4] The case to which they refer, described in our case report, is unusual in that the neck of the pseudoaneurysm (arising from the brachial artery in a child) was of similar diameter to that of the vessel. This is why we advise that it is essential to assess the diameter and length of the pseudoaneurysm neck before thrombin injection. We recommend that, should the neck be anything other than a pinpoint source, then balloon occlusion should be considered.

1 Carroll JF, Moskowitz K, Edwards NM, *et al*. Immunological assessment of patients treated with bovine fibrinogen as a haemostatic agent. *Thromb Haemost* 1996;**76**:925–31.
2 Chonhan VD, De la Cadena RA, Nagaswamic C, *et al*. Simultaneous occurrence of human antibodies directed against fibrinogen, thrombin and factor V following the exposure to bovine thrombin: effects on blood coagulation, platelet C activation and platelet function. *Thromb Haemost* 1997;**77**:343–9.
4 Muntean W, Zenz W, Edlinger G, *et al*. Severe bleeding due to factor V inhibitor after repeated operations using fibrin sealant containing bovine thrombin. *Thromb Haemost* 1997;**77**:1223.
5 Lennox A, Griffin M, Nicolaides A, *et al*. Regarding "Percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms". *J Vasc Surg* 1998;**28**:1120–1.

Mobile intracardiac calcinosis: risk of thromboembolism in patients with haemodialysed end stage renal disease

EDITOR,—Tsuchihashi and colleagues describe a number of interesting cases of mobile cardiac calcinosis in dialysis patients complicated by systemic thromboembolism.[1] However, in their discussion of possible pathophysiological mechanisms they fail to mention the possible roles of a number of calcification regulatory proteins called Gla proteins. This is a potentially important omission as it may affect management decisions regarding anticoagulation with warfarin.

Work from our laboratory and others has revealed that calcification in the vasculature is not simply a passive degenerative process as was previously thought.[2 3] On the contrary it seems to be a highly complex and regulated process as in bone. Attention has focused on a number of proteins which appear to have regulatory roles during the calcification process and in particular on a group of these proteins known as Gla proteins.[4] These Gla proteins are so named because they contain an uncommon amino acid—gamma carboxyglutamic acid (Gla)—formed by a vitamin K dependent post-translational modification of specific glutamic acid residues. The Gla residues appear to confer calcium binding properties to these proteins. One of the Gla proteins—matrix Gla protein—is thought to act as an inhibitor of calcification since it has been found in intimate association with areas of calcification, and mice lacking this gene have rampant vascular calcification.[5]

Since metabolic defects in chronic renal failure do not fully explain the presence of extraskeletal calcification, a role for these calcification regulatory proteins is clearly possible. In addition there is in vitro as well as in vivo data from both humans and rats that inhibition of the vitamin K dependent process of Gla residue formation by warfarin may be deleterious, leading to an increase in calcification.[6–8]

We feel there are sufficient data to exercise caution in the use of warfarin for the prevention of thromboembolism in the presence of critical extraskeletal and vascular calcification such as in the cases described by Tsuchihashi and colleagues, where any further increase in calcification could potentially be very harmful. Alternative anticoagulation strategies such as low molecular weight heparins may be more prudent until the basic mechanisms underlying the regulation of calcification are better understood. Whether long term warfarin treatment in general leads to any adverse

effects such as increases in arterial, aortic or mitral annular calcification is worthy of investigation.

A FARZANEH-FAR
C SHANAHAN
D PROUDFOOT
PL WEISSBERG
Division of Cardiovascular Medicine, University of Cambridge, Addenbrooke's Hospital (ACCI level 6), Hills Road, Cambridge CB2 2QQ, UK

1 Tsuchihashi K, Nozawa A, Marusaki S, *et al*. Mobile intracardiac calcinosis: a new risk of thromboembolism in patients with haemodialysed end stage renal disease. *Heart* 1999;**82**:638–40.
2 Wexler L. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association writing group. *Circulation.* 1996; **94**:1175–92.
3 Proudfoot D, Shanahan CM, Weissberg PL. Vascular calcification: new insights into an old problem [editorial; comment]. *J Pathol* 1998; **185**:1–3.
4 Shanahan CM, Proudfoot D, Farzaneh-Far A, *et al*. The role of Gla proteins in vascular calcification. *Crit Rev Eukaryot Gene Expr* 1998;**8**:357–75.
5 Luo G, Ducy P, McKee MD, *et al*. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 1997;**386**: 78–81.
6 Proudfoot D, Skepper JN, Shanahan CM, *et al*. Calcification of human vascular cells in vitro is correlated with high levels of matrix Gla protein and low levels of osteopontin expression. *Arterioscler Thromb Vasc Biol* 1998;**18**: 379–88.
7 Coates T, Kirkland GS, Dymock RB, *et al*. Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis* 1998;**32**:384–91.
8 Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. *Arterioscler Thromb Vasc Biol* 1998;**18**:1400–7.

The letter was shown to the authors who reply as follows

As pointed out by Farzaneh-Far and colleagues, many heterogeneous factors such as non-collagenous proteins (Gla protein and vitronectin in atherosclerosis plaques; osteopontin, vitronectin and osteocalcin in cardiac valve calcification), hypertension and aging, diabetes, excess vitamin D3 use, and calcium and phosphate imbalance through hypo- or hyperparathyroidism has been postulated as a possible cause of rapid calcinosis of the cardiovascular system in end stage renal disease.[1–3] Recently, Price and colleagues in rats[4] and Coates and colleagues in patients with calcific uraemic arteriopathy[5] reported the possibility of warfarin related cardiovascular calcification in relation to non-collagenous proteins, Gla.

We do think that the possible contributions of non-collagenous proteins to the rapid cardiovascular calcifications in end stage renal disease should not be neglected in our case studies; however, warfarin has not been prescribed in our cases before obtaining echocardiographic diagnosis. Therefore, warfarin use will not be the main cause of rapid calcinosis, at least in our series of cases. Moreover, in case 2 of our study,[6] a surgical specimen revealed fresh red thrombus attaching to cardiac calcinosis, and any kind of anticoagulation treatment will be essential clinically for preventing short term thromboembolism. Indeed, low molecular weight heparin might be a better therapeutic option in these circumstances, but it also has a limitation in long term clinical use. At this point, monitoring calcium–phosphate imbalance and the changes of calcinosis size, warfarin use for preventing thromboembolism will be the most conventional drug treatment in cardiac calcinosis of end stage renal disease. Further studies should be conducted on the cause of rapid cardiac calcinosis and the possibility of warfarin having a deteriorating effect on cardiovascular calcinosis.

1 Tsuchihashi K, Takizawa H, Torii T, *et al*. Hypoparathyroidism potentiates cardiovascular complications through disturbed calcium metabolism: possible risk of vitamin D3 analog administration in dialysis patients with end-staged renal disease. *Nephron* In press.
2 Christian RC, Fitzpatrick LA. Vascular calcification. *Curr Opin Nephrol Hypertens* 1999;**8**: 443–8.
3 Proudfoot D, Skepper JN, Shanahan CM, *et al*. Calcification of human vascular cells in vitro is correlated with high levels of matrix Gla protein and low levels of osteopontin expression. *Arterioscler Thromb Vasc Biol* 1998;**18**: 379–88.
4 Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. *Arterioscler Thromb Vasc Biol* 1998;**18**:1400–7.
5 Coates T, Kirkland GS, Dymock RB, *et al*. Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis* 1998;**32**:384–91.
6 Tsuchihashi K, Nozawa A, Marusaki S, *et al*. Mobile intracardiac calcinosis: a new risk of thromboembolism in patients with haemodialysed end stage renal disease. *Heart* 1999;**82**: 638–40.

Instantaneous pressure–flow velocity relations of systemic venous return in patients with univentricular circulation

EDITOR,—We read with great interest the article by Kaulitz *et al* where Doppler measurements of various venous flows were performed with simultaneous respiratory and venous pressure recordings.[1] The main findings were: venous flow and pressure are dependent on respiration in total cavopulmonary connection (TCPC); and venous flow and pressures are cardiac dependent in atriopulmonary connection (APC).

While the authors should be commended for monitoring simultaneous flow and pressure data along with respiratory and cardiac monitoring, there were no new insights. Venous flow in the TCPC, by the nature of dissociation with the atrial hydraulic function, has been shown to be augmented largely during inspiration when the further decrease of the negative intrathoracic pressures "draws" inferior venous flow antegrade.[2–4] While venous flow in APC will show less respiratory effect as it is coupled with the atria, it has also long been known to be related to the cardiac cycle.[2 5 6]

Important new information might have been gathered by the authors if more subtle pressure–flow velocity relations in TCPC and APC had been described. Theoretically, the relation between pressure and flow allows evaluation of pathway resistance or vascular impedance, properties of the Fontan circulation that may be crucial to its efficiency.

We also have some methodological concerns; the use of maximal velocity as an indicator of flow can be misleading. As flow is related to the integration of velocity and time, it is dependent on duration of flow. In other words, it is possible to have high maximal velocity but low flow rate if the Doppler velocity time integral is small. This is especially true when the spectral profile is not symmetrically parabolic. Furthermore, as the venous flow in both APC and TCPC exhibited retrograde patterns, the use of maximal antegrade velocity does not take this into account and therefore would not reflect the net or total flow during inspiration or expiration.

Finally, in the evaluation of the haemodynamics of the venous system, particularly in a Fontan circulation devoid of a ventricular hydraulic source, hydrostatic forces may play important roles. Recently we have examined the effect of gravity during an investigation of infradiaphragmatic venous return using Doppler ultrasonography to evaluate flow rates. Our preliminary results show, for example, that gravity exerts a significant influence on both the splanchnic and systemic inferior venous flow dynamics.[7] There are many additional haemodynamic variables that may influence these Fontan circulations, and further studies must concentrate on these more subtle, but perhaps just as important, relations in the future.

T-Y HSIA
S KHAMBADKONE
A N REDINGTON
M R DE LEVAL
Cardiothoracic Unit, Great Ormond Street Hospital for Children, London WC1N 3JH, UK
email: hsia@welchlink.welch.jhu.edu

1 Kaulitz R, Bergman P, Luhmer I, *et al*. Instantaneous pressure-flow velocity relations of systemic venous return in patients with univentricular circulation. *Heart* 1999;**82**:294–9.
2 Arisawa J, Morimoto S, Ikezoe J, *et al*. Pulsed Doppler echocardiographic assessment of portal venous flow patterns in patients after the Fontan operation. *Br Heart J* 1993;**69**:41–6.
3 Penny DJ, Redington AN. Doppler echocardiographic evaluation of pulmonary blood flow after the Fontan operation: the role of the lungs. *Br Heart J* 1991;**66**:372–4.
4 Redington AN, Penny D, Shinebourne EA. Pulmonary blood flow after total cavopulmonary shunt. *Br Heart J* 1991;**65**:213–17.
5 DiSessa TG, Child JS, Perloff JK, *et al*. Systemic venous and pulmonary arterial flow patterns after Fontan's procedure for tricuspid atresia or single ventricle. *Circulation* 1984;**70**:898–902.
6 Qureshi SA, Richheimer R, McKay R, *et al*. Doppler echocardiographic evaluation of pulmonary artery blood flow after modified Fontan operation: importance of atrial contraction. *Br Heart J* 1990;**64**:272–6.
7 Hsia TY, Khambadkone S, Migliavacca F, *et al*. Effects of respiration and gravity on infradiaphragmatic venous flow in normal and Fontan patients [abstract]. 72nd American Heart Association Scientific Sessions, Atlanta, Georgia, November 1999.

Surgery for aortic stenosis in severely symptomatic patients older than 80 years: experience in a single UK centre

EDITOR,—There are limitations to the use of increases in serum creatinine as a marker indicative of early postoperative death,[1], not least because derangement in this parameter may have more to do with injudicious diuretic dosage in the presence of the unique co-existence of diastolic left ventricular failure and left ventricular outflow obstruction. The use of diuretics for antifailure treatment may, in this context (as in other conditions characterised by diastolic failure), impair the left ventricular filling to such an extent as to precipitate a low output state,[2] one consequence being the development of prerenal uraemia. Therefore, if anything, the onset of deterioration in renal function should initiate a shift from medical treatment to surgical intervention, coupled with an interim reduction in diuretic dosage. Surprisingly, notwithstanding the acknowledgement of the existence of an aortic stenosis related syndrome of

low output failure (characterised by pronounced fatigue and debilitation),[3] there is little or no documentation that one of its manifestations could be the syndrome of "aggravated renal dysfunction during intensive treatment for advanced chronic heart failure".[4]

OMP JOLOBE
Department of Medicine for the Elderly, Tameside General Hospital, Fountain Street, Ashton under Lyne, OL6 9RW, UK

1 Gilbert T, Orr W, Banning AP. Surgery for aortic stenosis in severely symptomatic patients older than 80 years: experience in a single UK centre. *Heart* 1999;**82**:138–42.
2 Kessler KM. Heart failure with normal systolic function. *Arch Intern Med* 1988;**148**:2109–11.
3 Braunwald E. Aortic stenosis, clinical manifestations. In: Braunwald E. *Heart disease*, 3rd ed. Philadelphia: WB Saunders, 1988:1055–7.
4 Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999;**138**:285–90.

Flying after heart surgery

EDITOR,—The editorial "Flying after heart surgery",[1] is timely and focuses on an important aspect of rehabilitation. One might, however, question the validity of the statement that "Pilots may see cardiac surgery as their only hope...". Furthermore, in attempting to explain "the 1% rule", the defining point between professional fitness to fly on multicrew operations and permanent unfitness for duty, the authors' statements need some clarification.

The 1% rule[2] requires that the cardiovascular mortality rate of an airman should not exceed 1% per annum, or approximately one event/one million hours. This attrition is approximately that of a 65 year old man in northern Europe and will be encumbered by additional non-fatal co-morbid, but potentially incapacitating, events. It does not rely, as Treasure and Janvrin have stated,[1] on the impossible incapacitation rate of one event in 1 000 000 000 hours. This figure is the aviation industry target for the "very remote" possibility of an unpredicted (that is, mechanical) catastrophe leading to a fatal accident,[3] and is also the target multicrew fatal accident rate attributable to incapacitation of one of the pilots.[3] Employing the 1% rule, and making the assumption that only 10% of the envelope of a flight of average duration (100 minutes) is vulnerable with a 1% chance of an event during the vulnerable period leading to an accident,[4] the probability of a multicrew accident because of a cardiovascular cause is in the order of 1 in 1 000 000 000 hours, a target the industry is on course to achieve.

The most recent and currently used protocols for recertification following cardiac surgery, which are published in the Joint Aviation Requirements—Flight Crew Licensing Part 3 (medical),[5] for Europe, require a post index event (surgery, angioplasty, myocardial infarction) delay of six months before recertification can be considered. This differs from the figures derived from the older publications that are quoted by your contributors. Those requiring the text of the JAR-MED, or advice, may write to the Chief Medical Officer, Medical Division, Civil Aviation Authority, Gatwick, West Sussex RH6 0YR, or to the Joint Aviation Authorities, PO Box 3000, 2130KA, Hoofdorp, Netherlands. An up to date bibliography on the subject (not cited) is included in the Second European Workshop in Aviation Cardiology.[6]

MICHAEL JOY
St Peters Hospital Guildford Road Chertsey Surrey KT16 0PZ, UK

1 Treasure T, Janvrin S. Flying after heart surgery [editorial]. *Heart* 1999;**82**:3–4.
2 Tunstall-Pedoe H. Cardiovascular risk and risk factors in the context of aircrew certification. *Eur Heart J* 1992;**13**(suppl H):16–20.
3 Chaplin J. In perspective in the safety of aircraft, pilots and their hearts. *Eur Heart J* 1988; **9**(suppl G):17–20.
4 Chapman PJC. The consequences of inflight incapacitation in civil aviation. *Aviat Space Environ Med* 1984;**55**:497–500.
5 *Joint aviation requirements*. JAR-FCL 3. Flight crew licensing (medical). 28 Feb 1997.
6 Joy M, ed. The second european workshop in aviation cardiology. *Eur Heart J* 1999;**1**(suppl): D1-131.

The letter was shown to the authors who reply as follows:

Our editorial in *Heart* does discuss an aspect of rehabilitation after cardiac surgery, albeit a very narrow one. Pilots often do see cardiac surgery as their only hope of regaining a licence to fly, and in this context we consider our statements to be valid.

We are not sure that Professor Joy's clarification of the 1% rule adds much to what we wrote on a "need to know" basis for cardiac surgeons. Both he and we state the same thing. To the travelling public, a reassuringly small chance (1 in 1 000 000 000 hours of flying) of a pilot's incapacitation leading to a fatal aircraft accident is met by that pilot (and the co-pilot) having less than a 1% risk of a myocardial event in a year.

We then set out the post surgery criteria that must be achieved to meet that risk. These are the criteria published in the current European Joint Aviation Requirements,[1] which states that ". . .subjects may be considered for recertification [after coronary artery surgery] not sooner than nine months after surgery . . .".

As a footnote, both Professor Joy and ourselves serve on the Civil Aviation Authority Medical Advisory Panel. This might indicate to your readers that reaching a panel consensus about a pilot's fitness to fly is seldom easy.

1 *Joint aviation requirements*. JAR-FCL 3. Flight crew licensing (medical). 28 Feb 1997.

Radial coronary angiography and stenting

EDITOR,—We were interested in Mann's editorial on radial coronary angiography and stenting, but disagree with one aspect.[1] Mann states that "the discomfort of catheter removal is less than for the femoral approach". This is the opposite of our own and others' experience using the same equipment.[2 3] He adds that "the morbidity of the procedure is less, and patients prefer the radial approach". In support of this claim, he quotes Kiemeneij's ACCESS study,[4] (which merely alludes to unpublished data on procedural comfort) and Cooper *et al* who used mechanical compression for femoral haemostasis.[5] He fails, however, to draw attention to similar studies which have shown the opposite—that in addition to being a more technically challenging procedure (with lower success rate and longer procedure duration), the radial approach is more painful.[3 6]

In addition to this, the limitations of the radial approach are not adequately discussed. Access failure, radial artery spasm, hypotension or bradycardia are seen in up to 20% of cases, and may be serious.[2] We believe (certainly for coronary angiography) that the radial approach should be reserved for patients in whom the femoral approach is relatively contraindicated.

DAVID HILDICK-SMITH
MARTIN LOWE
MICHAEL PETCH
Cardiac Unit, Papworth Hospital, Cambridge CB3 8RE, UK

PETER LUDMAN
Department of Cardiology, Heartlands Hospital, Birmingham B9 5SS, UK

1 Mann T. The radial approach for coronary angiography and stenting. *Heart* 1999;**82**:411–12.
2 Hildick-Smith DJ, Lowe MD, Walsh JT, *et al*. Coronary angiography from the radial artery—experience, complications and limitations. *Int J Cardiol* 1998;**64**:231–9.
3 Grinfeld L, Berrocal D, Matas CR, *et al*. What is the most effective vascular approach for a diagnostic cardiac catheterization? A randomized trial using the femoral brachial or radial approaches [abstract]. *J Am Coll Cardiol* 1996; **27**:17A.
4 Kiemeneij F, Laarman GJ, Odekerken D, *et al*. A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the ACCESS study. *J Am Coll Cardiol* 1997;**29**: 1269–75.
5 Cooper CJ, El-Shiekh RA, Cohen DJ, *et al*. Effect of transradial access on quality of life and cost of cardiac catheterization: a randomized comparison. *Am Heart J* 1999;**138**: 430–6.
6 Ludman PF, Stephens NG, Harcombe A, *et al*. Radial versus femoral approach for diagnostic coronary angiography in stable angina pectoris. *Am J Cardiol* 1997;**79**:1239–41.

This letter was shown to the author, who replies as follows:

The use of verapamil to prevent radial artery spasm has been one of the most important advances in the development of the transradial technique. Earlier studies, including those cited by Dr Hildick-Smith *et al*, used only nitrates, or sublingual nifedipine, or both to prevent such spasm, and verapamil is a substantially more effective agent.[1] The intra-arterial administration of 3–5 mg has an immediate onset of action without systemic side effects and should be given before sheath advancement.

The radial artery is extremely sensitive to circulating catecholamines.[2] Thus, spasm may be provoked or accentuated by anxiety and pain in addition to mechanical manipulation. In this regard, the importance of adequate sedation and analgesia cannot be overemphasised. Other tips regarding management of radial artery spasm can be found on Dr Kiemeneij's website (www.radialforce.org).

The above preventive measures have virtually eliminated the problems noted by Dr Hildick-Smith *et al.* The incidence of radial artery access failure should be less than 5%.[3 4]

1 He GW. Verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with paraverine solution. *J Thorac Cardiovasc Surg* 1998; **115**:1321–7.
2 He GW, Yang CQ. Characteristics of adrenoreceptors in the human radial artery: clinical implications. *J Thorac Cardiovasc Surg* 1998; **115**:1321–7.
3 Mann, T, Cubeddu G, Bowen J, *et al*. Stenting in acute coronary syndromes: a comparison of radial versus femoral access sites. *J Am Coll Cardiol* 1998;**32**:573–6.

4 Mann T, Cowper P, Peterson E, *et al.* Transradial coronary stenting: comparison with femoral access closed with an arterial suture device. *Catheter Cardiovasc Intervn* [in press].

Pre-excitation or post-excitation

EDITOR,—We read with great interest the case study by Lau *et al* entitled "A new ECG sign of an accessory pathway in sinus rhythm: pseudo partial right bundle branch block".[1] However, ventricular pre-excitation can change any part of QRS; the sole terminal portion change is very rare.[2] In the demonstrated case, the authors stated that the pseudo partial right bundle branch block was the only manifestation of the left sided accessory pathway. However, in the V3 leads, the PR seems to be shortened and the initial portion of QRS complexes can be interpreted as delta waves (fig 1).

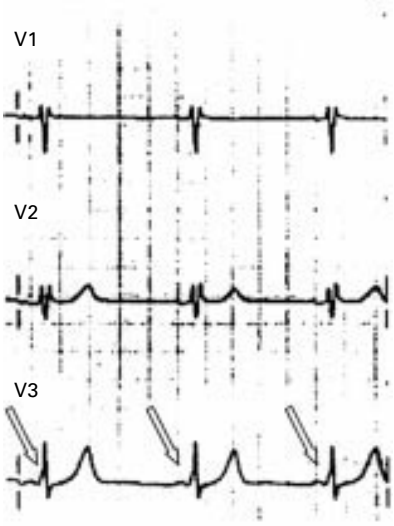

Figure 1 In lead V3, the arrows indicate the delta waves with short PR intervals.

We think that the demonstrated case was not a post-excitation but a pre-excitation with discrete ECG signs.

JÁNOS TOMCSÁNYI
JÓZSEF TENCZER
National Korányi Institute, Budapest, Hungary

1 Lau EW, Ng GA, Griffith MJ. A new ECG sign of an accessory pathway in sinus rhythm: pseudo partial right bundle branch block. *Heart* 1999;**82**:244–5.
2 Tenczer J, Littmann L, Fenyvesi T, *et al.* Procainamide induced unusual changes of the terminal QRS vectors in patients with and without pre-excitation. In Antalóczi Z, ed. *Modern electrocardiology*, Amsterdam, Akadémia-Exerpta Medica 1978:493.

This letter was shown to the authors who reply as follows:

The pseudo partial right bundle branch block we propose is a subtle manifestation of left ventricular *pre*-excitation and not *post*-excitation, even though the ECG feature occurs only in the *terminal* part of the QRS complex. The slight slurring in the upstroke of the QRS complex in V3 in the pre-ablation ECG alluded to by Tomcsányi and Tenczer was still present in the post-ablation ECG, proving that it was not part of the manifestation of ventricular pre-excitation.

On the management of scorpion stings

EDITOR,—We read with great interest Karnad's paper,[1] and also the responses in the correspondence columns[2] concerning the same article. We have the following points to make based on our 12 years' experience of scorpion envenomation in experimental animals.

According to Karnad's study,[1] scorpion envenomed patients exhibited haemodynamic changes in terms of right or left ventricular failure. However, our results with experimental animals have shown two stages of envenomation—namely, a stage of immediate respiratory failure and a delayed stage of circulatory failure.[3] Respiratory failure occurred within two to three minutes in all 10 of the animals we studied. Nearly 40% of them died within five minutes; the remaining 60% recovered from the initial respiratory arrest and survived for a further two to three hours. In this 60%, however, respiration never returned to normal, and it was associated with ischaemia-like ECG patterns. At the same time, the mean arterial pressure gradually decreased until it dropped abruptly along with respiratory arrest. Eventually, ventricular fibrillation occurred resulting in the animal's death. The initial stage appears to be mediated by the neuronal components, as reported elsewhere.[4] The circulatory failure may be due to increased kinins decreasing the blood pressure, or to irreversible shock syndrome associated with multiorgan failure, or myocardial ischaemia leading to ventricular failure. At this stage, we have observed increased secretions (lacrimation, salivation, and tracheal secretion), passing of urine and stool, etc. Our results indicate that respiratory failure is more critical in determining the mortality and time of death than circulatory failure.

We are not able to comprehend the exact mechanisms by which captopril reverted the circulatory derangements and the improvement of scorpion stung patients.[1] Rather, we anticipated a fall in blood pressure with captopril, as it increases endogenous kinin concentrations. We have showed that captopril mimicks the action of venom.[4] However, Karnad[1] and Bawaskar[5] missed our reports on *Buthus tamulus* envenomation.[4 6 7] Further, it has also been shown that kallikrein-kinin inhibitor (aprotinin) countered the scorpion toxicity.[4 6 8] In addition, we have shown that scorpion venom increased the afferent vagal activity that can be blocked by aprotinin.[6] This evidence indicates that aprotinin blocks the underlying pathology of scorpion envenomation, and is therefore better than other drugs for treating envenomation. Prasozin, an α_1 adrenergic receptor blocker, can only block the increased adrenergic activity seen after envenomation at the postsynaptic sites, but it cannot reverse the underlying pathology generated by kinins or other mediators. Contrarily, there are reports of the successful use of insulin[9 10] in patients stung by scorpions, and these reports do not find a place in the discussions of Karnad[1] or Bawaskar.[5] Therefore, we feel that insulin still has a place as a therapeutic agent in the treatment of scorpion toxicity unless disproved otherwise.

Regarding pulmonary oedema associated with scorpion envenomation, we have recently demonstrated pulmonary oedema after *Buthus tamulus* envenomation (detected by physical and histological evidence).[11] Further, pulmonary oedema was due to the involvement of kinins as pretreatment and aprotinin, which blocked the venom induced pulmonary oedema and other features of scorpion toxicity.[11] The decreased ventilation seen at this stage of delayed circulatory failure further favours the formation of pulmonary oedema.

In conclusion, captopril should be avoided in the treatment of scorpion toxicity until we understand the precise mechanisms behind its action. Aprotinin is a better choice as it blocks or counters the pathophysiological processes of scorpion envenomation and is also easily available in developing countries like India, where antivenom has yet to find a place in the market. The proven efficacy of insulin has to be considered with greater openness for the benefit of scorpion stung patients.

S B DESHPANDE
A B ALEX
Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India
email: desh@banaras.ernet.in

1 Karnad DR. Haemodynamic pattern in patients with scorpion envenomation. *Heart* 1998;**79**:485–9.
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This letter was shown to the author and Dr Bawaskar responds as follows:

Our experience and rational approach to the management of life threatening, acute medical emergencies caused by scorpion envenomation is entirely different, and we do not agree with the use of aprotinin advocated by Deshpande and Alex. Aprotinin is not available in India; it is currently only licensed

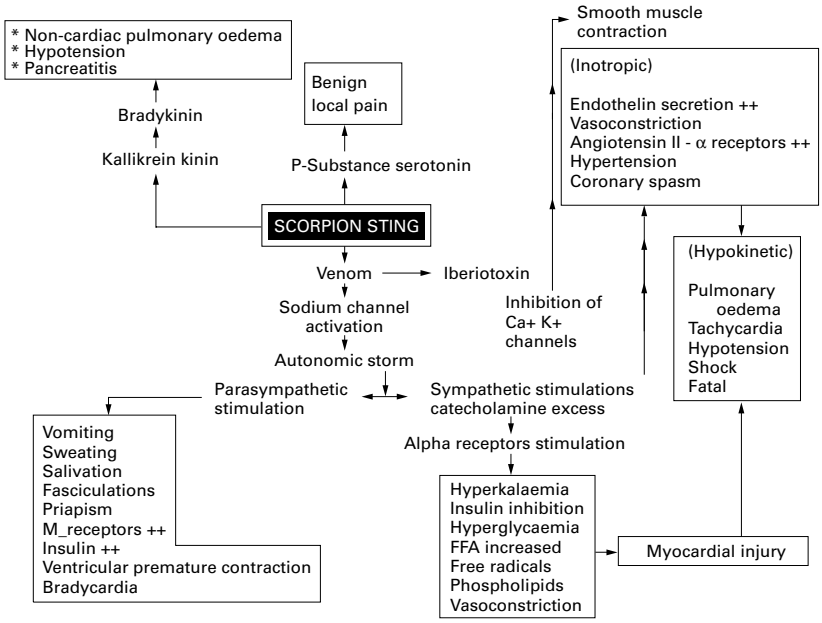

Figure 1 Pathophysiology of scorpion sting.

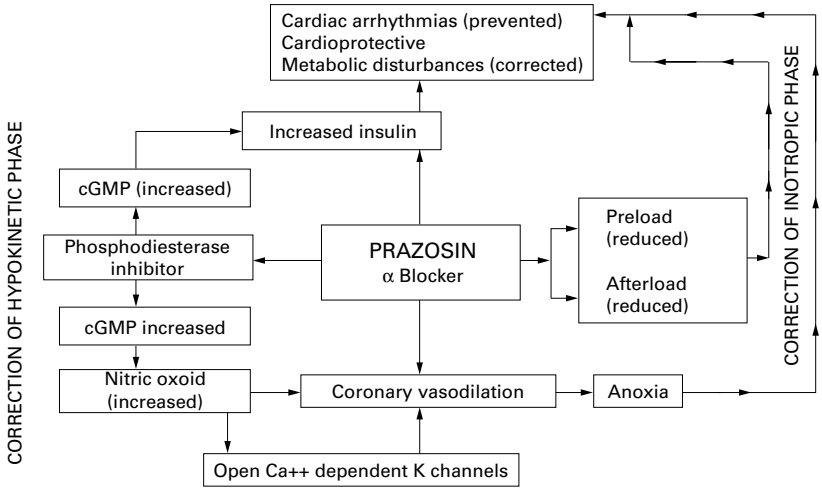

Figure 2 Effects of prazosin (venom antidote).

for cardiac operations that have a large risk of perioperative bleeding. In human scorpionism, which is entirely different from experimental, the clinical manifestations are related to many factors such as the weight of the victim, the size of the scorpion, the season, and the time lapsed between sting and administration of prazosin.[1] By the time they are hospitalised, all patients exhibit some cardiovascular manifestations, many have full blown pulmonary oedema.[2] We have been treating scorpion sting victims since 1976, and have treated more than 1500 severe cases. In our series, no victim had respiratory depression, arrest, or cardiac arrhythmia once prazosin had taken effect.[3] Respiratory failure is a secondary phenomenon.[4]

Scorpion venom stimulates neuronal sodium channels, resulting in autonomic storm. Both branches of the autonomic system are stimulated, resulting in vomiting, sweating, salivation, fasciculations, priapism in men, hypotension, hypertension, bradycardia or tachycardia, ventricular premature contractions, cool extremities, pulmonary oedema, and shock (fig 1).[2]

It has been proved beyond doubt that pulmonary oedema, as a result of scorpion envenomation, is due to myocardial dysfunction.[5] Bradykinin induced secretory pulmonary oedema is secondary, and occurs as a result of the stimulation of kalikrenin due to tissue damage caused by anoxia and the accumulation of oxygen free radicals, if cardiogenic manifestations are not managed earlier with prazosin.[6]

α Receptor stimulation plays an important role in the pathogenesis of scorpion stings resulting in an inotropic (hypertension) phase, which, if not treated, progresses to a hypokinetic (pulmonary oedema, hypotension, tachycardia, and shock) phase. The hypokinetic phase is due to the liberation of oxygen free radicals, fatty acids, and insulin deficiency.[3] Prazosin enhances insulin secretion by blocking α receptors over β cells of the pancreas. Hyperkalaemia and hyperglycaemia exist in the victim due to autonomic storm. Prazosin increased endogenous insulin secretion thus acts like a glucose–insulin potassium drip and protects and prevents myocardium injury caused by liberated fatty acids and oxygen free radicals, and prevents lethal cardiac arrhythmia and sudden death (fig 2).[7]

Atropine, which is similar to aprotinin, enhances cardiovascular morbidity and mortality by blocking acetyl choline action (vagolytic).[8]

Recently, Abroug *et al* reported that scorpion antivenom is no better than placebo.[9] Similarly, in our series, scorpion antivenom (available since 1997) did not prevent cardiovascular manifestations as a result of *Mesobuthus tamulus* sting.[10] Primary care doctors need full understanding of pathophysiology and a rational approach to this type of medical emergency to avoid high morbidity and mortality.

Prazosin, a pharmacological antidote to venom, which reverses both inotropic and hypokinetic phases induced by severe scorpion stings, is simple, scientific, easily available, and does not cause anaphylaxis. Since its advent, mortality due to scorpion stings has been reduced to less than 1%. It should be the first line of treatment for severe scorpion stings.[11]

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Dr Carey Coombs and his non-existent cardiac infarct

EDITOR,—Carey Franklin Coombs, 1879–1932, was a physician at the Bristol General Hospital. He made important studies of rheumatic fever describing the diastolic murmur of acute rheumatic mitral valvulitis, which bears his name, and taking a great interest in the prevention and management of heart disease in children. His 1924 monograph *Rheumatic heart disease* became a standard work on the subject. He also did pioneering work in coronary heart disease, and around 1910 he made a clinical

diagnosis of coronary thrombosis at a time when the condition was almost unheard of. His patient survived, so without necropsy proof he did not achieve priority of recognition, which went to James Herrick of Chicago in 1912.[1] His interest in the disease continued, and by 1932 he had studied and published 144 cases of coronary thrombosis.[2]

His own illness

In 1932, aged 53, he stopped with chest pain while walking up a steep hill. A short time later, he had an unheralded syncopal attack and was admitted to hospital. On recovery he had no pain. The ECG showed bundle branch block and a diagnosis of coronary thrombosis was made. As was then the rule, he was kept in bed for six weeks. He was then allowed up, but suddenly fell down dead.

Carey Coombs's medical registrar at that time was C Bruce Perry (1903–96), who later became the professor of medicine in Bristol. It was he who told me about Coombs's illness and its aftermath. On the day before the funeral, Mrs Coombs asked Perry to remove her husband's heart saying that it had been his wish to have it placed in the pathology museum. By then the body was in a coffin in Coombs's consulting room, but Perry unscrewed the lid and took out the heart with the help of a postmortem technician. Perry, a young registrar aged 29, was then presented with a dilemma that he later wrote about: "Externally the heart looked normal. I did not know what to do, or to say to the people who had looked after him. Geoffrey Hadfield [then pathologist at Barts having been previously in Bristol] was coming to the funeral so I phoned him and he agreed to 'demonstrate' the heart to the senior physicians afterwards. This he did showing them an infarct that was not there but they were satisfied. When they had gone he gave me the heart and said 'now find out what was wrong'. We took sections of all parts histologically and finally found a small lesion in the region of the AV bundle. I am afraid there was nothing to put in the museum. Looking back on it I think he had a Stokes-Adams attack when he fell unconscious and a massive pulmonary embolism when he died. But of course we did not examine the lungs so we shall never know. One should not agree to a partial incomplete examination if one wants to get as near as possible to the truth" (personal communication).

Another domiciliary necropsy done by Bruce Perry

One of the cases in the 1932 paper[1] was a man whom Carey Coombs had seen in the patient's home in 1928, in consultation with the general practitioner. There was then no portable ECG to support the clinical diagnosis. The patient died and Perry recounted that he was sent to get the heart: "I took knives etc from the postmortem room and lots of old newspapers. The body was lying on a bed and as I lifted it onto the floor covered in newspapers a wig fell off. The general practitioner was present and said, 'Oh dear, I have known him all these years and did not know he had a wig.'" The heart when opened showed a classic infarct which Coombs had photographed, but apparently never published.

An excellent and full account of Carey Coombs's life and work has been written by Clive Weston,[1] and his influence lives on in Bristol with a research scholarship named after him.

A HOLLMAN
Sea Bank, Chick Hill,
Pett Level, East Sussex TN35 4EQ, UK

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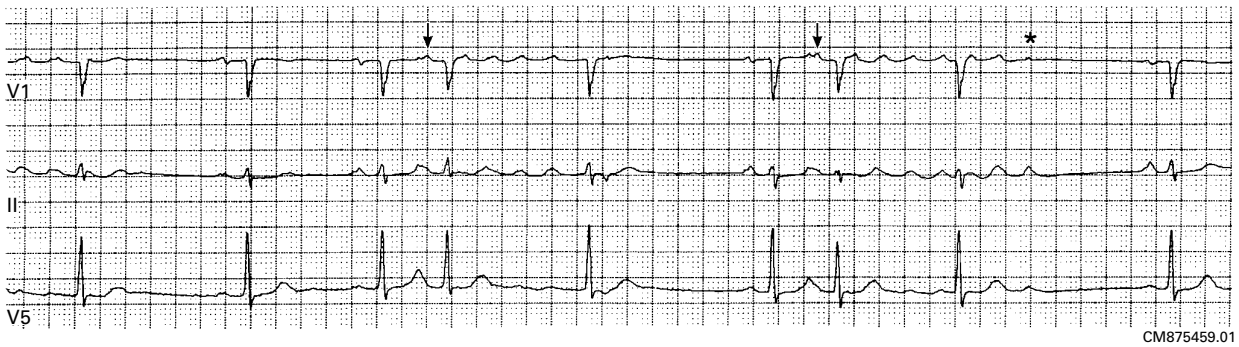
IMAGES IN CARDIOLOGY

Onset and termination of atrial fibrillation

Ectopic atrial activity may be a mechanism of onset of some forms of atrial fibrillation (AF). This ECG from a 77 year old man shows triggering and termination of AF. AF is present at the start but rapidly terminates. During sinus rhythm atrial extrasystoles (arrows) reinitiate short bursts of AF. A third atrial extrasystole (*) is not conducted. The P wave morphology and axis of the triggering ectopic beats suggested focal activity close to the right superior pulmonary vein. During a treadmill exercise test AF was initiated by an atrial extrasystole and sustained for 16 minutes. Subsequent Holter monitoring revealed frequent atrial ectopy (239 per hour) and 11 episodes of AF lasting from a few seconds to 4.8 minutes. No other aetiology for AF was found. Recognition of this focal mode of onset of AF in the otherwise normal heart is important since radiofrequency ablation is potentially curative.

THOMAS C GERBER
PETER A BRADY
JOSEPH L BLACKSHEAR



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